CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-142

CHEMISTRY REVIEW(S)

DIVISION OF DERMATOLOGIC AND DENTAL PRODUCTS DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-142 CHEM. REVIEW #: 1 REVIEW DATE: 12 MAY-00 MAY 19 2000

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	28-JUL-99	29-JUL-99	24-AUG-99
AMENDMENT/AC	15-SEP-99	16-SEP-99	27-SEP-99
AMENDMENT/BC	27-OCT-99	01-NOV-99	10-NOV-99
AMENDMENT/BC	03-FEB-00	07-FEB-00	10-FEB-00
AMENDMENT/BL	04-FEB-00	07-FEB-00	Review # 2
FAX	12-MAY-00	12-MAY-00	12-MAY-00

NAME & ADDRESS OF APPLICANT:

CONNETICS CORPORATION
3400 West Bayshore Road
Palo Alto, CA 94303

Claire Lockey,
Vice President, Regulatory Affairs
(650) 843-2800

DRUG PRODUCT NAME:

Proprietary:	OLUX Foam, 0.05%
Nonproprietary/USAN:	Clobetasol Propionate Foam
Code Names/#'s:	MP-123456B
Chemical Type	Fluorinated Glucocorticoid
Therapeutic Class:	3S

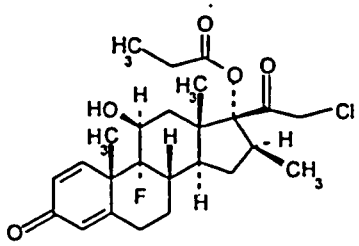
Patent Status: (Clobetasol) German Patent Number 1,902,340 U.S. Patent Number 3,721,687 (1969, 1973, both to Glaxo); U.S. Patent Number 4,370,322 (Glaxo), expired on 27 January 1991.

PHARMACOLOGICAL CATEGORY/INDICATION: [redacted]

DOSAGE FORM:	Foam
STRENGTHS:	0.05%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	_X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT, CAS NUMBER:

- 21-Chloro-9-fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17 propionate;
- (11β,16β)-21-Chloro-9-fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17 propionate;
- (11β,16β)-21-Chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-pregna-1,4-diene-3,20-dione



MOLECULAR FORMULA: $C_{25}H_{32}ClFO_5$
MOLECULAR WEIGHT: 466.98
CAS NUMBER: 25122-46-7 (25122-41-2 for underivatized clobetasol)

SUPPORTING DOCUMENTS:

- NDA 20-934, LUXIQ™ (betamethasone valerate) foam, 0.12%, Connetics Corporation, approved on February 28, 1999.
- [redacted] meeting on February 19, 1998). Results of clinical studies presented at a pre-NDA meeting on April 26, 1999).
- [redacted], Type II DMF; bulk drug substance manufacturer (clobetasol propionate). [redacted] Letter of authorization for FDA access dated March 4, 1998, signed by [redacted] Last update: January 29, 1999. Date of last review (acceptable): April 12, 1999.
- [redacted] Type II DMF, [redacted] Reviewed by Ernie Pappas in January 2000 (acceptable).
- [redacted] Type III DMF, can manufacturer. [redacted] Letter of authorization for FDA access dated June 24, 1999, signed by [redacted] Not reviewed.

RELATED DOCUMENTS:

The following are cited but no Letter of Authorization is provided:

- [redacted]
- NDA 19-322, Temovate Cream, 0.05%, Glaxo-Wellcome, approved in 1985.
- NDA 19-323, Temovate Ointment, 0.05%, Glaxo-Wellcome, approved in 1985.
- NDA 19-966, Temovate Scalp Application, 0.05%, Glaxo-Wellcome, approved in 1990.
- NDA 20-337, Temovate Gel, 0.05%, Glaxo-Wellcome, approved in 1994.
- NDA 20-340, Temovate E Cream, 0.05%, Glaxo-Wellcome, approved in 1994.

CONSULTS:

OPDRA was consulted concerning the proposed trade name, the large icon next to the trade name, and the use of [redacted] The applicant subsequently "withdrew" the icon in an amendment dated February 4, 2000. The proposed trade name was acceptable. [redacted], however, was not acceptable because it is too close (in pronunciation) to the commercially available OTC topical drug, "Vioform" (see attachment 1).

REMARKS/COMMENTS:

Clobetasol propionate, a synthetic analog of prednisolone, is currently approved for topical use in the US in five different dosage forms (see supporting documents above): cream, ointment, gel, solution, and emollient cream. All the latter are at the same strength of 0.05% as that proposed by the applicant. The applicant also markets LUXIQ Foam (NDA 20-934), a recently approved drug product. The excipients, container/closure system and propellant are identical in both drug products, but the active ingredient is different. Both drug products are manufactured and released under contract at the same manufacturing and drug product release sites.

[redacted]

CONCLUSIONS & RECOMMENDATIONS:

The application is **APPROVABLE** for manufacturing and controls under section 505 of the Act. The two manufacturing facilities for the drug substance were inspected and found to be acceptable. The amended shelf life of 24 months [redacted] is acceptable.
The applicant should be informed in the action letter that in all future stability testing, the stability protocol should provide for storing the can in both the upright and inverted positions.

Prior to final CMC approval the following need to be addressed:

a) Satisfactory response to the information requests including clarification of certain aspects of the applicant's post approval stability commitment.

b) modification of the label as per Chemistry Review # 2 and its addenda.

/S/ 5/19/00

Saleh A. Turujman, Ph.D.
Review Chemist

cc: Orig. NDA 21-142
HFD-540/Division File
HFD-540/DivDir/JWilkin
HFD-540/SATurujman/5/2/00
HFD-540/MO/MOkun
HFD-540/Pharm/PBrown
HFD-540/Micro/DRiley
HFD-540/PM/KBhatt
HFD-540/ChemTmLdr/WHDeCamp WD 5/19/00

Not entered into DFS

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APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

14 pages

DIVISION OF DERMATOLOGIC AND DENTAL PRODUCTS DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

APR 20 2000

NDA #: 21-142 CHEM. REVIEW #: 2 REVIEW DATE: 20-APR-00

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	28-JUL-99	29-JUL-99	Review # 1
AMENDMENT/AC	15-SEP-99	16-SEP-99	Review # 1
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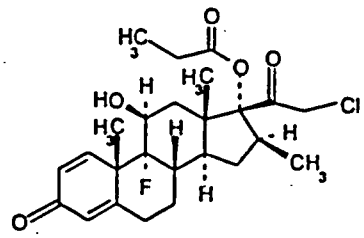

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SUPPORTING DOCUMENTS:

See review # 1

RELATED DOCUMENTS:

CONSULTS:

OPDRA was consulted concerning the trade name, the use of — ' and the large icon next to the trade name. The applicant subsequently "withdrew" the icon in an amendment dated February 24, 2000. The tradenname was acceptable but — was not because it is too close to a current topical drug, "Vioform" (NDA 20-934).

REMARKS/COMMENTS:

This labeling review was conducted at the request of the program manager to be presented at the OLUX labeling day, April 24, 2000

CONCLUSIONS & RECOMMENDATIONS:

The chemistry reviewer's corrections are in italic font on a copy provided by the applicant of the draft labeling, the carton label and the container label (See attacments 1, 2, and 3). The modifications are self explanatory: Recommended text deletions are denoted by a strikeout, and additions are shaded in grey.

1st

Saleh A. Turujman, Ph.D.
Review Chemist

4/20/00

cc: Orig. NDA 21-142
HFD-540/Division File
HFD-540/DivDir/JWilkin
HFD-540/SATurujman/4/20/00
HFD-540/MO/MOkun
HFD-540/Pharm/PBrown
HFD-540/Micro/DHussong
HFD-540/PM/KBhatt
HFD-540/ChemTmLdr/WHDecamp 4/20/00

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4/27/00 - Minor changes in labeling memo of 4/24/00.

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 9

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Draft Labeling
(not releasable,